REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

Upon entry of this amendment, claims 34-73 will be pending in this application and presented for examination. Claims 1-18 and 20-33 have been canceled without prejudice to renewal. New claims 35-73 have been added. Claim 34 has been amended to include the proper spelling of "propionate." Claim 34 is allowable pursuant to the Office Action mailed November 1, 2002.

New independent claims 35 and 51 recite "an emulsifier component in an amount wherein the ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent is about 1:5 to 1:8." Support for this feature is found, for example, on page 5, lines 16-18; and the examples on page 7, (formulae 1-7). Claims 36-50 depend from claim 35.

New independent claims 52 and 69 recite "a pharmaceutical aerosol foam composition consisting essentially of..." Support is found in the originally filed claims, and on page 2, lines 9-18. Claims 53-68 depend from claim 52. Claim 70 depends from claim 69.

New independent claim 71 recites a pharmaceutically active ingredient that is a corticosteroid. Support is found, for example, on page 3, lines 1-3.

New dependent claim 72 recites "an emulsifier component in an amount of from approximately 1 to 15% by weight, based on the total weight of the composition." Support is found, for example, in originally filed claim 12, and on page 5, lines 18-21.

New independent claim 73 is based upon allowable claim 34 with further support found, for example, on page 4, lines 5-8.

In view of the foregoing support, Applicant believes no new matter has been introduced with the foregoing new claims and amendments. Reconsideration is respectfully requested.

II. CLAIM REJECTIONS STATED IN OFFICIAL ACTION DATED NOVEMBER 1, 2002

Rejection of Claims 1-18 and 20-33 under 35 U.S.C. § 112, New Matter Rejection.

In the interest of furthering prosecution of the present application, Applicant has canceled claims 1-18 and 20-33 without prejudice to renewal. Applicant believes the new claims obviate the new matter rejection.

Rejection of Claims 1-10, 12-14, 16-18, 20-26, 28-30 and 32-33 under 35 U.S.C. § 103(a) as allegedly obvious over Davis 5,143,717 in view of Woodford, et al. (J. Pharm Sci. (1977) 66:1).

As the Examiner is well aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

Applicant respectfully traverses this rejection because, absent impermissible hindsight reconstruction, there is no suggestion or motivation to combine Davis with Woodford. Further, the combined disclosures of Davis and Woodford do not teach or suggest, either explicitly or inherently, each and every element of the claimed invention.

No suggestion or motivation to combine Davis and Woodford

If [a] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. M.P.E.P. § 2143.01 (citing *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984)).

The Examiner states that Davis does not disclose or suggest an active ingredient which is insoluble in both water and the occlusive agent (page 7 of Paper No. 20). The Examiner states that it would have been obvious to modify the topical antibacterial foam of Davis by

adding corticosteroids as taught by Woodford, allegedly because of the expectation of obtaining a quick-break foam composition which could be used to deliver skin treatment compositions in a safe, economic way (pages 7-8 of Paper No. 20). Applicant respectfully asserts that the Examiner's proposed combination of adding Woodford's corticosteroids to Davis's topical foam would render the Davis foam unsatisfactory for its intended purpose. The Davis foam is not intended to be a quick-break foam, and requires a pharmaceutical agent that is linear and more hydrophilic at one end and more hydrophobic at the other.

The Davis foam requires a linear, amphipathic pharmaceutically active agent.

Davis states that the chemical structure of silver sulfadiazine, the antibiotic used in his foam, is linear, with one end being more hydrophilic than the other (*see*, column 2, lines 54-57 of the Davis patent). Davis further states that his specific formulation and methods result in a foam with an intricate bubble architecture resembling a micelle. *Id.* at column 2, lines 62-66. Davis also describes how a precise mixing of constituents is necessary to achieve the particular micellar architecture of his foam. *Id.* at column 3, lines 41-68. Davis's foam is so adapted to the linear and amphipathic character of silver sulfadiazine that claim 1 of the Davis patent is drawn to a water soluble foam containing "an antibiotic having molecules of generally linear structure with one end thereof being more hydrophilic than the other, with the other end being more hydrophobic." *Id.* at column 6, lines 44-54.

In order to secure allowance of U.S.P.N. 5,143,717, Davis submitted a Rule 132 Declaration, dated July 10, 1991[1], that explains the indispensable relationship of the linear and amphipathic structure of silver sulfadiazine to the stable and micellar characteristics critical to his foam for burn patients. Davis declares that he had achieved "a stable micellar structure with the silver sulfadiazine molecules, used as a "*lock and key mechanism*," being oriented perpendicularly (radially) throughout the very small bubble membranes with the water soluble ends thereof directed outwardly" (*see*, page 3, lines 20-24 of the Rule 132 declaration of Richard Davis, emphasis added). Davis also declares that "the silver sulfadiazine acted as a "*lock and key mechanism*" by providing less random motion of the material which constituted the membrane of

[1] Applicant submitted a copy of Richard Davis's Rule 132 Declaration with the response dated May 1, 2003.

the bubble....the silver sulfadiazine appears to control the entropy of the system." *Id.* at page 4, lines 6-10, emphasis added. Further, Davis declares that:

> By utilizing the "lock and key mechanism" of the silver sulfadiazine molecule, a linear, relatively straight, chain entity with a water soluble end and a lipid soluble end to provide a coupling at the gas/oil/water suspension interface (the wall of the bubble) and to reduce the mobility of those substances at that point, the stability of the foam has been experimentally observed to increase tremendously. This "locking" by the silver sulfadiazine molecule reduces the mobility of other substances at that point and therefore maintains the integrity of the surface of the bubbles, i.e. the formation of stable bubbles. *Id.* at page 4, line 18 through page 5, line 2.

Based on information in the Davis patent and Davis's Declaration, the Davis foam was developed specifically to deliver silver sulfadiazine as a clinically water soluble composition. If the Davis foam can accommodate any other pharmaceutically active agents, it is expected that such agents must at least be linear and amphipathic. The corticosteroid drugs disclosed by Woodford may or may not be more hydrophilic at one end, but the cholesterol core structure of a corticosteroid is certainly not linear. Rather than controlling the entropy of a lipid bilayer, a steroid, like its cholesterol core structure, would be expected to **separate** and **disperse hydrophobic tails**, thereby introducing fluidity to the inner regions of a lipid bilayer (*see*, Chapter 5.3 of Lodish, *et al.*, (2000) Molecular Cell Biology, 4th ed., W.H. Freeman & Co., New York, excerpt provided). As such, it is unlikely that any steroid could replace silver sulfadiazine in Davis's foam and achieve the "lock and key mechanism" critical to maintaining its stability and intricate micellar structure. Therefore, based upon the foregoing passage in Lodish, *et al.*, it is believed the steroid drugs disclosed by Woodford are unsuitable for the intended purposes of Davis's foam.

Applicant further notes that Davis's foam was developed specifically to deliver silver sulfadiazine as a clinically water soluble composition. Without this active ingredient, Davis's foam would not exist. In the present invention, the composition will form a foam with or without an active ingredient.

The Davis foam is not intended to be a quick-break foam.

An important feature of the Davis foam is that it remains stable over long periods of time (*see*, column 4, lines 19-22 of the Davis patent). Davis's statements in his Declaration demonstrate that Davis literally intended for the foam to remain in a foam state, and not collapse, like a quick-break foam. On page 3, line 25 through page 5, line 2 of the Davis Declaration, Davis states that his foam **does not collapse**, and that the "lock and key mechanism" by which silver sulfadiazine apparently controls the entropy of the system is critical to the increased stability of his foam. By combining Davis with Woodford to obtain a quick-break foam, the Examiner is attempting to create a foam that the inventor of the primary reference explicitly did not intend, thereby rendering the primary reference **unsatisfactory** for its intended purpose.

Therefore, Applicant respectfully requests that the Examiner withdraw the rejection.

Failure to teach or suggest all claim limitations

Applicant maintains that the Davis and Woodford references are improperly combined. However, even if combined, the combination of Davis and Woodford fails to disclose or suggest all the elements of the claimed foam compositions and dispensers.

Canceled claims 1-18 and 20-33 have been replaced with new claims 35-72. New independent claims 35 and 51 recite "an emulsifier component in an amount wherein the ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent is about 1:5 to 1:8." New independent claims 52 and 69 recite "a pharmaceutical aerosol foam composition consisting essentially of..."

Neither Davis nor Woodford disclose the claimed formulation ratios.

Applicant maintains that the modification the Examiner has contemplated render Davis **unsatisfactory** for its intended purpose. However, a *prima facie* case of obviousness has not been established because neither Davis nor Woodford disclose or suggest a foam composition containing an emulsifier component in an amount wherein the ratio of emulsifier

component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent is about 1:5 to 1:8.

If one follows Davis's definition of the components in his formulations, then Davis discloses foam compositions with a ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent that is about 1:1. For instance, from the table in the Davis patent in columns 5-6, the Example I formulation contains 8.22 + 4.38 + 0.55 = 13.15 % by weight emulsifier, and 8.22 % occlusive agent + 1.00 % silver sulfadiazine + 0.0 % organic cosolvent (propane and isobutene are propellants). In the Example I formulation, for every 1 % emulsifier, there is 0.70 % occlusive agent, pharmaceutically active ingredient, and organic cosolvent (a 1:0.70 ratio). By analogous calculations, the "high range" Example I formulation is about 1:0.70 and the Examples VI-XV formulation is 1:0.68-0.88.[2]

Adding Woodford does not cure the deficiencies of Davis, because Woodford does not disclose an occlusive agent. However, if Polawax A31 emulsifying wax can be considered an occlusive agent, and not just a foaming agent as Woodford states on page 103, the quick-break foam formulation described on pages 99-100 of the cited Woodford manuscript discloses a formulation with a ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent of about either 1:4 or 1:25, depending on whether the dehydrated alcohol is considered an organic cosolvent (dichlorodifluromethane and dichlorotetrafluoroethane are propellants). Based upon the way Woodford uses the formulation components and if dehydrated alcohol is not considered an organic cosolvent, then the Woodford formulation contains 2.0 g emulsifying wax + 0.025 % corticosteroid + 5.5 % organic cosolvent (propylene glycol). This is a ratio of 1 % by weight of emulsifier for every 3.76 % of a combination of the occlusive agent, pharmaceutically active

[2] The foregoing categorization of components is based upon Applicant's understanding of their functions. In certain instances, propylene glycol for example, can be considered an emulsifier. By including it in the calculation as an emulsifier, the Davis foams effectively have about a 2:1 ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent. For instance, the Example I formulation contains 4.38 + 0.55 + 8.22 + 3.83 = 16.98 % emulsifier components, and 8.22 % occlusive agent + 1.00 % silver sulfadiazine + 0 % organic cosolvent. This is a ratio of 1.84 % emulsifier components for every 1 % of a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent (a 1.84:1 ratio). By analogous calculation, the "high range" Example I formulation is 1.9:1 and the Examples VI-XV formulation is 1.5:1 (*see*, table in columns 5 and 6 of the Davis patent).

ingredient, and organic cosolvent (a 1:3.76 ratio). If the dehydrated alcohol is considered an organic cosolvent, then the Woodford formulation contains 5.50 g propylene glycol and 2.0 g emulsifying wax + 0.025 % corticosteroid + 43.77 % organic cosolvent (dehydrated alcohol has a density of 0.789 g/ml). This is a ratio of 1 % by weight of emulsifier for every 25.65 % of a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent (a 1:25.65 ratio)[3].

Because the ratios of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent disclosed in the foam compositions of either Davis or Woodford are not 1:5 to 1:8 as is currently taught and claimed, their combined disclosures do not teach or suggest a ratio of 1:5 to 1:8. Therefore, neither Davis nor Woodford disclose or suggest all of the recited elements of claims 35-51.

The Davis formulation requires additional elements.

Independent claims 52 and 69 recite "a pharmaceutical aerosol foam composition consisting essentially of an effective amount of a pharmaceutically active ingredient, an occlusive agent, an aqueous solvent, and an organic cosolvent." By reciting the language "consisting essentially of," claims 52-70 exclude additional components that substantially change the claimed foam compositions, such as a humectant or an emollient.

The Davis foam compositions are intended to be stable and water soluble for the application and easy removal from burn victims' injured skin. This is reflected in the formulations detailed in the table in columns 5 and 6 of the Davis patent that not only include emulsifier components as a major proportion of the foam composition, but also require a

---

[3] If propylene glycol is considered an emulsifier and if dehydrated alcohol is not considered an organic cosolvent, then the Woodford formulation contains 5.50 g propylene glycol emulsifier component and 2.0 g emulsifying wax + 0.025 % corticosteroid + 0 % organic cosolvent. This is a ratio of 2.7 % by weight of emulsifier for every 1 % of a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent (a 2.7:1 ratio). If the dehydrated alcohol is considered an organic cosolvent, and propylene glycol is considered an emulsifier, then the Woodford formulation contains 5.50 g propylene glycol emulsifier component and 2.0 g emulsifying wax + 0.025 % corticosteroid + 43.77 % organic cosolvent (dehydrated alcohol has a density of 0.789 g/ml). This is a ratio of 1 % by weight of emulsifier for every 8.3 % of a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent.

humectant and an emollient component. The humectant is necessary because Davis states that it is an important feature of his foam to retain a large proportion of water, yet remain stable over long periods of time. (*see*, column 4, lines 19-24 of the Davis patent). An emollient, isopropyl myristrate, is also included as a necessary element in all of Davis's formulations. *Id.* at column 2, lines 20-27, column 4, lines 5-17 and the table in columns 5 and 6. Claim 1 of the Davis patent also requires an emollient and a humectant. *Id.* at column 6, lines 59-62.

Adding Woodford does not give Davis any reason to exclude a humectant or an emollient in his foam formulations. In Woodford's formulations, the addition of a particular moisturizer decreased delivery of corticosteroid (*see*, page 102 of Woodford). But removing either the humectant or the emollient from the Davis foams destroys Davis's intended purpose, because his foam would no longer retain a large proportion of water or remain stable over long periods of time (*see*, column 4, lines 19-24 of the Davis patent). Applicant respectfully asserts that nothing in Davis or Woodford, alone or combined, teaches or suggests a foam including an effective amount of a pharmaceutically active ingredient, an occlusive agent, an aqueous solvent, an organic cosolvent, and optionally an emulsifier component, without also including an additional humectant and an additional emollient. Therefore, neither Davis nor Woodford disclose or suggest all of the recited elements of claims 52-70. As such, Applicant respectfully requests that the Examiner withdraw the rejection.

Rejection of Claims 1-14, 16-18, 20-30 and 32-33 under 35 U.S.C. § 103(a) as allegedly obvious over Davis 5,143,717 in view of Woodford, et al. (J. Pharm Sci. (1977) 66:1) and Jones, et al., WO 96/27376.

The Examiner further cites the Jones application to combine with Davis and Woodford because Jones discloses a foam composition containing polysorbate 60 as an emulsifier component. Applicant respectfully asserts that Jones does not cure the deficiencies of Davis and Woodford and the combination of Davis, Woodford and Jones still do not recite all the required elements of the claims, including new dependent claims 44 and 62.

Jones does not teach or suggest a foam composition with a ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and

organic cosolvent that is about 1:5 to 1:8. Jones does not teach or suggest an occlusive agent. If the humectant, propylene glycol, is not considered an emulsifier component, the Jones foam formulations have a ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent that is about 1:30 when ethanol is considered an organic cosolvent 2.0 % / (0.12 % betamethosone valerate + 57.79 % ethanol + 0% occlusive agent) (*see*, page 8 of the Jones application)[4]. Therefore, the inclusion of Jones in combination with Davis and Woodford fails to disclose or suggest all the required elements of the claimed foam compositions in claims 35-51.

Additionally, Jones discloses on page 4, lines 12-14, of the Jones application that "it is preferred to add a humectant to reduce the drying effects of the aqueous aliphatic alcohol." Therefore, the addition of Jones supports the disclosure of Davis for including an additional humectant in a foam formulation, especially if the ethanol component disclosed in Woodford and Jones is included in the composition. The inclusion of Jones combined with Davis and Woodford still does not disclose or suggest a foam including an effective amount of a pharmaceutically active ingredient, an occlusive agent, an aqueous solvent, an organic cosolvent, and optionally an emulsifier component, without also including an additional humectant and an additional emollient. Therefore, the combination of Davis, Woodford and Jones do not disclose or suggest all of the recited elements of claims 52-70.

Rejection of Claims 1-10, 12-18, 20-26 and 28-33 under 35 U.S.C. § 103(a) as allegedly obvious over Davis 5,143,717 in view of Woodford, et al. (J. Pharm Sci. (1977) 66:1) and Gers-Barlag, et al. 5,833,960.

The Examiner further cites the Gers-Barlag patent to combine with Davis and Woodford because Gers-Barlag discloses using C_{12-15}-alkyl benzoate in the oil phase of the preparation for a sunscreen after-foaming composition. Applicant respectfully asserts that combining Gers-Barlag with Davis destroys the purposes of Davis, the primary cited reference.

[4] If propylene glycol is considered an emulsifier component, then the Jones foam formulations have a ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient, and organic cosolvent that is either about 20:1 or 1:24, depending on whether ethanol is considered an organic cosolvent ((0.4 % + 2.00 % propylene glycol / 0.12 % or (0.4 % + 2.00 %) / (0.12 % + 57.79 %)).

Further, the inclusion of Gers-Barlag does not cure the deficiencies of Davis and Woodford and the combination of Davis, Woodford and Gers-Barlag still do not recite all the required elements of the claims, including new dependent Claims 48 and 66.

No suggestion or motivation to combine Gers-Barlag with Davis and Woodford

An after-foaming composition, such as that disclosed in the Gers-Barlag patent is incompatible with the intended purpose of Davis, which is to provide a foam "that may be easily quickly and relatively painlessly applied to abrasions or burns and is essentially water soluble to permit easy removal with a minimum of pain to the patient" (*see*, column 1, lines 56-60 of the Davis patent). An after-foaming preparation, such as that disclosed by Gers-Barlag, requires rubbing on the skin at the point of application to initiate foam formation (*see*, column 8, line 64 through column 9, line 2 of the Gers-Barlag patent). Therefore, application of an after-foaming preparation would be conceivably painful to a patient having burns or abrasions, and is unsatisfactory for its intended purpose of Davis.

Furthermore, water solubility is of primary importance to the Davis foam formulations (*see*, column 1, lines 56-60 and column 4, lines 19-25 of the Davis patent). In the Davis formulations, the occlusive agent, emollient, foaming agent/emulsifier component (stearyl alcohol) and emulsifier agents are combined to form an oil phase. *Id.* at column 4, lines 26-30. An additional organic cosolvent, which would decrease water solubility, is not included. Adding the organic cosolvents of Gers-Barlag further renders the Davis foam formulations unsatisfactory for their intended purpose by impeding their required water solubility.

Failure to teach or suggest all claim limitations

The inclusion of Gers-Barlag does not cure the deficiencies of Davis and Woodford. Gers-Barlag does not teach or suggest a foam composition with a ratio of emulsifier component to a combination of the occlusive agent, pharmaceutically active ingredient that is insoluble in both water and the occlusive agent, and organic cosolvent that is about 1:5 to about 1:8. Gers-Barlag does not disclose an occlusive agent. Gers-Barlag discloses and claims water-

soluble, pharmaceutically acceptable UV filters (*see*, columns 5 and 6 and Claim 1, the only independent claim in the Gers-Barlag patent). Gers-Barlag does not disclose a pharmaceutically active ingredient being insoluble in both water and the occlusive agent. Gers-Barlag also discloses that "foams are normally only obtainable by using special surfactants whose compatibility with the skin is often poor" (*Id.* at column 4, lines 31-33). Gers-Barlag discloses using "surface-active" glucose derivatives and glycerol monocarboxylic or dicarboxylic acid monoesters in his after-foaming formulations (*Id.* at columns 5 and 6).

The only formulation of Gers-Barlag that discloses including C_{12-15}-alkyl benzoates is Example 5 in column 16 of the Gers-Barlag patent. If the inclusion of glyceryl stearate in the Example 5 after-foaming formulation is to be considered an emulsifier component, then the only ingredients relevant to the ratio calculation are glyceryl stearate and methyl glucose sequisterate as emulsifier components and octyldodecanol, caprylic/capric triglyceride and C_{12-15}-alkyl benzoates as organic cosolvents, because there is no occlusive agent nor a pharmaceutically active ingredient that is insoluble in both water and occlusive agent. For every 7.0 % by weight of emulsifier glyceryl stearate, the Example 5 formulation includes about 5.0 % of organic cosolvent (a 1:0.71 ratio). If the UV protectors are considered to be active ingredients (phenylbenzimidazolesulphonic acid 2.00% + tris-[aniline-(p-carbo-2'-ethyl-1'-hexyloxy)] triazine 3.00% + 4-(tert-butyl)-4'-methoxydibenzoylmethane 2.00% + 4-methylbenzylidenecamphor 2.00%, giving a total of 9.00% active, then the ratio would instead be 7% emulsifier : (5% cosolvent + 9% active + 0% occlusive), or a 1:2 ratio.

Applicant respectfully asserts that the Gers-Barlag Example 5 formulation adds nothing to the combined disclosures of Davis and Woodford, and that the combination of Davis, Woodford and Gers-Barlag still do not recite all the required elements of the Claims 35-51.

The Gers-Barlag Example 5 after-foaming formulation also discloses including the emollients methyl glucose sesquisterate and caprylic/capric triglyceride and the humectant butylene glycol. Like Jones and Woodford, the disclosure of Gers-Barlag also fails to teach or suggest not including the emollients or humectants as additional ingredients in the Davis burn treatment foams. Therefore, the combination of Davis, Woodford and Gers-Barlag still do not recite all the required elements of claims 52-70.

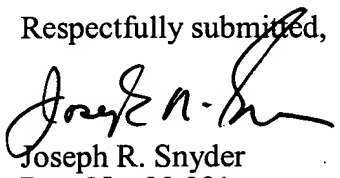
For the foregoing reasons, Applicant respectfully asserts that it is not possible for the combination of Davis and Woodford, further including Jones or Gers-Barlag to render the claimed invention obvious. Accordingly, the Examiner is respectfully requested to withdraw these rejections.

III. CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
JS:jlw
60000599 v1